PSJ17 Exh 57

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Tracie A. Parker
Senior Manager
Regulatory Affairs
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

RE: NDA # 20-747
Actiq® (oral transmucosal fentanyl citrate)
MACMIS ID # 12800

Dear Ms. Parker:

This letter responds to Cephalon, Inc's (Cephalon) submission dated October 21, 2004 requesting comments on proposed promotional materials for Actiq® (oral transmucosal fentanyl citrate). The Division of Drug Marketing, Advertising, and Communications (DDMAC) provides comments on the following proposed promotional materials:

- Actiq Spanish Warning Stickers (ACT224)
- Actiq Montage Journal Ad (ACT217)
- Actiq Detail Aid (203)

Since many claims and representations are similar or closely related, DDMAC's comments on a particular claim or representation apply to similar claims or representations in these and future promotional materials for Actiq.

Actiq Spanish Warning Stickers

We have reviewed the Actiq Spanish Warning Stickers and have no comments at this time.

Actiq Montage Journal Ad

Misleading Presentation of Information

You present the claim, "Patients can use ACTIQ anywhere, as soon as they begin to feel breakthrough cancer pain." This claim is misleading because it implies that it is appropriate for patients to consume as many Actiq units as needed to control all episodes of breakthrough cancer pain per day, when such is not the case. The PI specifically states, "Once a successful dose has been found..., patients should limit consumption to four or fewer units per day." Therefore, DDMAC recommends including adequate and prominent

context to avoid this misleading implication. We refer to our comment letters dated January 26, 1999 and September 9, 2004 regarding similar claims.

Overstatement of Efficacy

You present the claims, "When onset matters...ACTIQ® **responds**" and "**Relief** at hand" (emphasis added). These claims overstate the efficacy of Actiq because they imply that Actiq is guaranteed to provide adequate and effective response and pain relief for every patient every time the product is used, when such is not the case. We note that in your cover letter, you state, "...the tag line ["Relief at hand"] is balanced with "With ACTIQ, pain relief may be observed in 15 minutes. Patients may experience pain relief..." However, we remind Cephalon that misleading claims can not be corrected by true information relating to risk or efficacy. We refer to our comment letter dated January 26, 1999 regarding a similar issue.

You present the claim "Patients may experience relief while taking ACTIQ..." This claim is misleading because it implies that onset of action will occur at any time period following commencement of administration, which is inconsistent with the PI. The PI specifically states, "Actiq produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration." We refer to our comment letter dated June 17, 2004 regarding this similar claim.

Minimization of Risk

You present the claim, "The adverse events seen with ACTIQ are typical opioid side effects,..." This claim is misleading because Actiq is the only opioid approved with a risk management plan, and there are several prominent boxed warnings related to safety that appear in the approved labeling and that are exclusive to Actiq. Therefore, statements implying that the safety profile of Actiq is similar to other opioids are considered misleading because this presentation implies that Actiq is as safe as other opioids, when such has not been demonstrated by substantial evidence or substantial clinical experience. We refer to our comment letters dated January 26, 1999, February 24, 1999 and August 29, 2002 regarding this issue.

You present the header "Safety" prior to the section describing adverse events associated with Actiq. This heading is misleading because it frames this section to suggest that the information presented is related to Actiq safety (i.e., Actiq has been shown to be safe), when, in fact, this section discusses important risk information. Therefore, we recommend that you revise this header to clarify that important risk information is presented (i.e., "Risk Information").

Actiq Detail Aid

The above comments should also be applied to this proposed promotional piece. In addition, DDMAC has the following comments:

Risk Management Plan

According to section 5.3 of the Actiq Risk Management Plan (RMP), "Detail aids for Actiq will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all leave behind detail aids will also prominently display the detail flag." DDMAC recommends ensuring that this proposed detail aid is compliant with the RMP.

Omission of Important Risk Information

According to section 5.3 of the Actiq Risk Management Plan (RMP), "Detail aids for Actiq will emphasize the three key safety messages," which consists of Child Safety Messages, Proper Patient Selection Messages, and Prevention of Diversion and Abuse Messages. This detail aid is misleading because you fail to communicate any Prevention of Diversion and Abuse Messages.

Overstatement of Efficacy

You present the claim, "Duration of pain relief was found to be 1 hour (the last time measured) following completion of the ACTIQ unit." This claim is misleading because it implies that duration of pain relief of one hour following completion of the Actiq unit has been evaluated and all patients who use Actiq will have pain relief for one hour, when such has not been demonstrated by substantial evidence. The PI specifically states, "Actiq produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes **following administration**" (emphasis added). Therefore, claims of efficacy beyond 45 minutes after completion of the Actiq unit are inconsistent with the PI.

You present the claim, "Dosing and titrating to optimize **control**" (emphasis added). This claim of "control" is misleading because it implies that all patients will experience control of their breakthrough cancer pain with Actiq, which thereby overstates the efficacy of Actiq. We refer to our comment letter dated August 29, 2002 and September 9, 2004 regarding a similar issue.

General

You present the claim, "Highly lipophilic for rapid absorption across the oral mucosa with slower absorption from the GI tract." For consistency and completeness with the PI, we suggest that you clarify that it is the oral transmucosal dosage form that has these absorption characteristics.

You present the claim, "Patients started on 200 mcg titrated to a mean maintenance dose of 789 mcg" and "86% of patients were titrated to 400 mcg or higher." For consistency and completeness with the PI, we suggest that you also include the material fact, "Those patients over the age of 65 years titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients."

We refer to your cover letter where you request approval to modify the detail aid for future printings to change the number in "over 48 million units of ACTIQ have been prescribed"

without submission 30 days prior to dissemination. Approval is not granted as such claims are promotional and require verification.

If you have any questions, please contact me by facsimile (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 12800 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Jialynn Wang, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications